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Review

Pathophysiology of upper extremity muscle disorders

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Abstract

A review of the literature on the pathophysiology of upper extremity muscle disorders (UEMDs) was performed. An overview is given of clinical findings and hypotheses on the pathogenesis of UEMDs. The literature indicates that disorders of muscle cells and limitations of the local circulation underlie UEMDs. However, these disorders identified do not necessarily lead to symptoms. The following mechanisms have been proposed in the literature: (1) selective recruitment and overloading of type I (Cinderella) motor units; (2) intra-cellular Ca^{2+} accumulation; (3) impaired blood flow; (3b) reperfusion injury; (3.3c) blood vessel–nociceptor interaction; (4a) myofascial force transmission; (4b) intramuscular shear forces; (5) trigger points; (6) impaired heat shock response. The results of the review indicate that there are multiple possible mechanisms, but none of the hypotheses forms a complete explanation and is sufficiently supported by empirical data. Overall, the literature indicates that: (1) sustained muscle activity, especially of type I motor units, may be a primary cause of UEMDs; (2) in UEMDs skeletal muscle may show changes in morphology, blood flow, and muscle activity; (3) accumulation of Ca^{2+} in the sarcoplasm may be the cause of muscle cell damage; (4) it seems plausible that sub-optimal blood flow plays a role in pathogenesis of UEMDs; (5) since the presence of fiber disorders is not a sufficient condition for the development of UEMDs additional mechanisms, such as sensitization, are assumed to play a role.

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Keywords: Repetitive strain injury; Cumulative trauma disorders; Myalgia; Low-intensity contraction; Muscle pain

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1. Introduction

Insight into the physiological mechanisms involved in the development and perpetuation of musculoskeletal disorders is of great importance with respect to prevention, diagnosis, treatment and rehabilitation of these disorders. Upper extremity disorders include a heterogeneous group of specific and non-specific symptoms. A symptom is considered to be *specific* when: (1) it comprises a more or less fixed combination of signs; (2) testing results in a predictable reaction; (3) it is uniquely identified and described in the clinical scientific literature. Examples of such specific disorders are epicondylitis lateralis and carpal tunnel syndrome. If a certain symptom does not match the criteria mentioned above, the symptom is called non-specific [126]. This non-specificity of symptoms obviously leads to problems in operational definitions of disorders and in diagnostics. Varying definitions and diagnostic criteria have been proposed in the literature and recently an attempt towards standardization has been reported [126]. Upper extremity disorders comprise soft tissue disorders of the muscles, tendons, ligaments, joints, peripheral nerves, and supporting blood vessels [69,126]. In view of the wide range of disorders, affected tissues and symptoms, it is unlikely that a single pathophysiological mechanism can be identified. In fact there are a number of hypotheses on the physiological mechanisms behind the development of upper extremity disorders. The proposed mechanisms are not necessarily mutually exclusive, but might either play independent roles possibly leading to the same symptoms, or they might play complementary or interacting roles. This paper gives an overview of possible mechanisms; the scope is limited to the pathophysiology of upper extremity muscle disorders (UEMDs), *that is disorders of muscle tissue proper, excluding tendon disorders and disorders of the tendinous insertions*. Referring to pain as one of the main symptoms, these disorders are also indicated with the term ‘myalgia’. Note that symptoms indicative of muscle disorders have been considered by some authors as specific and conclusive for such disorders [144], whereas other consider these to be non-specific [126].

Hypotheses on pathophysiological mechanisms describe parts of assumed causal relationship between task requirements on one hand and the symptoms of

UEMDs on the other hand. A simple model describing this relationship is presented in Fig. 1.

Of course the model presents a strong simplification of the complex processes involved in the pathophysiology. This simplification was however, made on purpose, since added detail to a model like this, would quickly refer to, or be based on, a particular theory on the pathophysiology of UEMDs. Also the suggested linearity might be misleading, and in Section 4, we will give some indications on possible circular causation within the model. However, this simplification to a linear causal model provides a clear structure for grouping and interpreting the literature.

Comprehensive reviews of the epidemiology on UEMDs [2,7,14,16,42,89,126,128] have shown strong and consistent associations between exposures and UEMDs. Although well-designed epidemiological studies provide important information on possible causality, no solid proof for inferences about causality can be gained from these studies. Necessary condition for inferences on causality is the biological plausibility of the causal role of the exposure to a certain factor in the development of a disorder or disease [51]. Biological plausibility refers to an association being compatible with existing knowledge on biological mechanisms. Furthermore, understanding of these mechanisms could provide a basis for explaining the signs and symptoms manifested by patients and a sound foundation for rational clinical care and therapy [32].

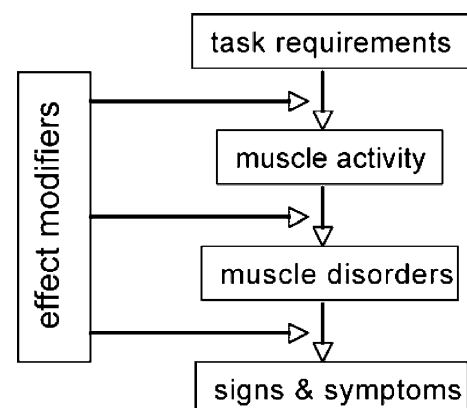


Fig. 1. Conceptual model of the pathophysiology of UEMDs.

The model implies that *symptoms* find their origin in *disorders of the muscle tissue*. Following the model backwards, the crucial question arises if and when muscle tissue disorders can result from *muscle activity*. Muscle activity depends on the human motor behavior, which comprises an extensive repertoire of postures, movements, and force exertion. In the model the human motor behavior is placed in the context of task performance and is seen as dependent on *task requirements*. Individual and contextual factors might, and are likely to, affect all described relationships. These factors are indicated in the model as *effect modifiers*. The multi-factorial nature of UEMDs is underlined by the influence of the effect modifiers. This review focuses on two questions: (1) Is there evidence that signs and symptoms of UEMDs are based on disorders of muscle tissue? (2) Can disorders of muscle tissue be caused by muscle activity of relatively low intensity? The relationship between task requirements and adverse patterns of muscle that we have recently reviewed elsewhere [24] is not specifically addressed.

2. Clinical findings: signs and symptoms

This section addresses the relationship between disorder and symptoms as indicated in the model of Fig. 1. It thus attempts to answer the first question formulated above. UEMDs appear to mainly affect the neck and shoulder muscles, in particular the descending part of the trapezius muscle [72,85,139]. Nevertheless, it has been suggested that surrounding musculature like the paravertebral musculature (the splenius capitis muscle, the rectus capitis muscle, the semispinalis capitis muscle and the longissimus capitis muscle) [126] and the levator scapulae muscle [71] can be affected as well. Also the forearm muscles, especially the extensor muscles, have been suggested to be quite frequently affected [111].

Among the more subjective symptoms of muscle disorders are sensations of constant muscle fatigue and stiffness, accompanied by radiating pain. These signs, combined with objective observations of increased muscle tone during passive movements, painful locations, and/or palpable discrete, focal, hyperirritable spots (trigger points) contribute to the diagnosis of UEMDs [99,144].

To obtain more insight into the underlying tissue disorders, additional objective information has been gathered using a variety of techniques. Early studies focused on fatigability of the muscles. Using electromyographic fatigue indicators several authors have shown more rapid development of fatigue in the descending part of the trapezius muscle in patients with UEMDs compared to healthy subjects [40,45,129]. Bjelle et al. [9,10] compared cases with acute, non-traumatic shoulder-neck pain to age- and sex-matched, paired controls. An increased blood concentration of creatine

kinase (CK), a marker of muscle damage, was found in a substantial part of the cases.

Biopsy studies have been used to study muscle fiber abnormalities. Muscle fibers characterized by the presence of zones lacking activity of some mitochondrial enzymes are indicated with the term ‘moth-eaten fibers’. Moth-eaten fibers have been regularly found in the trapezius muscle of myalgic patients [49,81,82] but also in control subjects [74,81]. The mitochondrial organization is disturbed in variable amounts of fibers in all trapezius muscles irrespective of whether they are from patients or control subjects. However, the level of disturbance is higher in symptomatic subjects [66,67].

Ten biopsy studies addressing structural and histochemical muscle fiber abnormalities related to muscle activity and myalgia have been reviewed, by Hägg [44]. Hägg included studies comparing two or three groups of subjects: (A) exposed with muscle complaints (myalgia); (B) healthy and exposed; (C) healthy and non-exposed. Exposed refers to the fact that subjects perform work that presumably causes this type of disorders. However, descriptions of work exposure have been vague or missing in most studies. In general a higher percentage of type I fibers was found in group A compared to group C. Increased fiber cross-sectional area of both types I and II fibers were found in groups A and B compared to group C. In spite of an increased number of capillaries per fiber, capillarization per fiber cross-sectional area was decreased in group A. This effect was found to be more pronounced in the group with more severe complaints. Some studies analyzed the content of the energy substrate ATP and the activity of the enzyme Cytochrome-c oxidase (COX) in the biopsies. These measures, reflecting the quality of metabolic homeostasis, differed between the groups. ATP content was lower in group A compared to group C and the number of fibers with no COX activity (COX negative fibers) was higher in groups A and B compared to group C. The occurrence of Ragged red fibers (RRFs), indicating structural damage to the cell membrane and mitochondria, was similar in group A and B and markedly less frequent in group C. So RRFs reflect the exposure to work but do not differentiate between patients and healthy subjects. Within group A, a relationship between the number of RRFs and the severity of complaints was found. It was noticed the RRFs are often COX negative fibers of type I.

Studies of the normal trapezius indicate a relatively poor supply of capillaries as well as low mitochondrial volume density as compared with limb muscles [83]. Since the mitochondrial volume density is directly related to oxidative capacity, the trapezius muscle has relatively low endurance capacity [6]. The presence of moth eaten fibers and RRFs indicates uneven distribution and proliferation of mitochondria. (Accumulation of mitochondria is seen in Gomori trichrome staining, and this

gives the ragged red appearance.) The mitochondrial proliferation might be a compensatory phenomenon in pathophysiological states affecting oxidative metabolism. RRFs appear to be related to insufficient blood supply, and may be induced by ischemia [47].

Indications that micro-circulation is locally decreased around fibers in the trapezius muscle of subjects with myalgic pain have been reported [75,77]. Furthermore, there are indications that arterial blood flow in subjects with a specific UEMDs differs from that in control subjects. Pritchard et al. [110] showed an impaired vasodilatation response of the brachial artery to forearm muscle activity in symptomatic subjects, resulting in a reduced blood flow. From the observation that hand temperature during typing increases more in controls than in symptomatic subjects, Sharma et al. [120] and Gold et al. [39] concluded that blood supply of the arm is diminished in patients, probably due to sympathetic dysregulation.

Rosendal et al. [114] found increased anaerobic metabolism during low-force exercise in patients with trapezius myalgia. The levels of metabolites associated with anaerobic metabolism correlated to pain intensity. Blood flow during the task was similar in patients and controls. Blood flow during a 20 min recovery period remained increased in the patients and returned to baseline in the controls. These results suggest that local circulation in the muscle may be reduced in the patients, while systemic blood flow is unaffected. A local limitation in blood flow due to inhomogeneous muscle activation (see also [115]) would then require prolonged hyperaemia in the recovery period. Note that the lack of difference in systemic blood flow is in contrast with findings of Pritchard et al. [110], which may be due to a different location of measurement.

In conclusion, indications have been found that disorders of muscle cells underlie UEMDs. Furthermore, limitations of the circulation play a role in these disorders, but is unsure whether this is a cause or consequence. It is clear that the disorders identified do not necessarily lead to symptoms. It cannot be excluded that reporting of pain occurs only when severity of the disorder, e.g., the numbers of affected muscle fibers, exceeds some unknown threshold value. However, it seems likely that several individual and environmental factors co-determine the reporting of symptoms, explaining the absence of a one-to-one relationship between disorder and pain or other symptoms. An extensive literature on pain processing exists that cannot be reviewed here but in the next paragraphs we will give some indications of such effect modification.

Pain, the most prominent symptom of UEMDs, is defined as an unpleasant sensory experience associated with actual or potential tissue damage. Pain is one of the somatic sensibilities with its own specialized set of neural pathways. Nociceptors are specialized receptors

that serve as injury (or noxious stimulus) receptors. Nociceptors are sensitive to chemical substances, released from damaged or overloaded cells, and excessive tissue deformation that may occur as a consequence of intramuscular connective tissue damage [98]. However, the experience of pain based on nociceptive information is subject to extensive modification based on both individual and contextual factors. For example, expectations about a nociceptive stimulus appear to strongly affect pain experience [109,117]. An important aspect in this respect is the fact that recurrent stimulation of nociceptors may induce sensitization, which means that the nociceptor threshold is lowered and the firing frequency in response to the same stimulus is increased (which is likely to be accompanied by an increased pain intensity). Sensitization is often accompanied by an increase of the sensitive area, leading to radiating pain [12,98]. A similar sensitization process occurs in the central nervous system (CNS), with substance P playing an important role. The concentration of this neurotransmitter, measured in the spinal cord, was increased in rats that had performed repetitive activities [4]. Central and/or peripheral sensitization may be required before serious pain is experienced, which would imply that symptoms are only reported after tissue disorder has been present for some time. In addition, these processes may be important determinants of severity and chronicity of pain.

Animal studies have shown cytokine release after low-intensity repetitive activities [3,1]. Besides their role in the inflammation process, cytokines have a large impact elsewhere in the body through effects on the CNS, leading to widespread physiological effects and even behavioral changes. Cytokines have for example been shown to influence illness related behavior, like inactivity [145,146] and may cause increased pain sensitivity [27,116]. As with nociceptive afference and pain, the relationships between cytokine concentrations on one hand and the symptom – sickness behavior – on the other hand is subject to effect modification by a range of factors. Interestingly, it has been shown in rats that motivation induced by environmental factors (cold exposure) could negate the inactivity induced by cytokines [23].

3. Pathophysiological mechanisms

This section deals with the transition from muscle activity to muscle disorders in the model of Fig. 1 and thus addresses our second research question. We first describe some animal experiments that indicate that muscle activity of low intensity can indeed cause tissue damage in muscles. As stated in the introduction it is not likely that a single comprehensive pathophysiological mechanism exists that is responsible for the tissue

damage and symptoms described. Several hypotheses on the pathogenesis have been put forward in the literature. We reviewed the literature on these hypotheses and give an overview of those mechanisms for which some experimental evidence has been provided either in the clinical literature or from animal experiments.

One of the most puzzling aspects of the pathophysiology of UEMDs is the fact that complaints can occur in individuals who perform low-intensity tasks, like computer work [137,138,150]. A commonly used indicator for muscle damage, the level of creatine kinase (CK), in blood was not found to be increased in such low-intensity tasks [93]. In contrast, increasing concentrations of CK, over a period of days, have been found during work with a high UEMD risk and a relatively high intensity [41,90].

Unaccustomed exercise involving stretch of active muscle at long length can cause extensive fiber damage, resulting in pain and tenderness [26,31,36,101]. Muscle damage has been shown to be greatest when large stretches at long sarcomere lengths occur [132]. This type of eccentric contractions is rare in low intensity activity and thus large effects are not expected. Therefore, this review will primarily focus on muscle damage due to concentric and isometric contractions. Note, however, that repeated eccentric contractions at short sarcomere lengths may be responsible in part for muscle damage in UEMDs [148]. Westerblad et al. [148] allude to repetitive, low-force contractions over prolonged times with co-contracting agonist and antagonist muscles as can be seen in the forearm during for example keying.

3.1. Evidence for muscle damage due to low-intensity loading

Animal experimental research has clearly shown that low-intensity loading can bring about muscle damage provided that the load imposed is static and of long duration. Lexell et al. [80] performed a study to determine effects of chronic low-frequency electrical stimulation on muscle fibers. Rabbit fast-twitch muscles, tibialis anterior and extensor digitorum longus, were stimulated for 9 days with pulse trains ranging in frequency from 1.25 to 10 Hz. After the higher stimulation frequencies, there was a significantly higher prevalence of degenerating muscle fibers. Moreover, muscles that had been subjected to continuous stimulation showed significantly more degeneration than muscles that had been stimulated intermittently (Fig. 2). A recent paper [3] described changes in motor skills and tissues of the upper extremity with regard to injury and inflammatory reactions resulting from performance of a voluntary forelimb repetitive reaching and grasping task in rats. Rats reached for food pellets at a rate of 4 reaches/min, 2 h/day, and 3 days/week for up to 8 weeks. The force

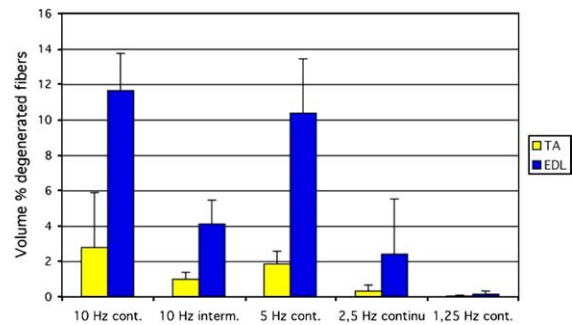


Fig. 2. Volume % degenerated fibers in rabbit muscles tibialis anterior (TA) and extensor digitorum longus (EDL) after several days of continuous and intermittent stimulation (data from [80]).

level involved in the grasping task was estimated at 1% of maximal force. Besides the fact that rats were unable to maintain baseline reach rate over the weeks, significantly more macrophages were found in the reach limb and serum levels of pro-inflammatory cytokines were increased. These results demonstrate that performance of low-intensity tasks can elicit responses associated with inflammation. However, in humans with UEMDs no acute inflammatory indicators have been found, but the presence of fibrotic tissue and anti-inflammatory mediators suggest a preceding inflammatory episode [5]. In conclusion, several animal experiments support the assumption that sustained low-intensity activity can cause muscle tissue disorders. The question to be addressed next, is how this can occur.

3.2. Cinderella hypothesis

The “Cinderella hypothesis” [43] can be seen as the most influential hypothesis for the development of muscle damage due to low-intensity tasks. In essence, this hypothesis focuses on the question when muscle activity of low intensity may become damaging. The considerations that led to the hypothesis did focus on the facts that the muscular force generated at sub-maximal levels engages only a fraction of the motor-units (MUs) available and that recruitment patterns are likely to be stereotypical [48,152]. The continuous activity of these MUs during sustained tasks was hypothesized to be the cause of damage to these MUs.

Hennemans [48] ‘size principle’ implies that small type I fibers are continuously activated during prolonged tasks. However, studies describing the recruitment of MUs show that in some subjects derecruitment of MUs occurs and that substitution of MUs takes place [29,97,149]. On the other hand, recent experiments did confirm the presence of continuous activity of some MUs in the trapezius muscle over a wide range of motor tasks [34,64,134,149,155]. Similar results were found with respect to the extensor muscles in the forearm [35]. Reported firing rates of these MUs for trapezius

muscle and extensor muscles are relatively high (10–20 Hz) [8,127,149] and comparable with firing rates of previously mentioned animal studies. The finding in the study of Lexell et al. [80] that especially muscles subjected to continuous stimulation are at risk for degeneration provides strong support for the “Cinderella hypothesis”.

Some epidemiological studies have shown that static muscle activity and a low rate of short unconscious interruptions in EMG activity (EMG gaps) are relevant for the development of complaints. Subjects in a group of manufacturing workers, who showed fewer EMG gaps in their trapezius muscle activity, were at higher risk to develop trapezius myalgia [137,138]. Such EMG gaps were found to coincide with derecruitment and substitution of MUs [149]. The relationship between the rate of EMG gaps and complaints could, however, not be found in office work [136]. A possible explanation could be that during office work periods of derecruitment occur anyway, which however, triggers the question why office workers would develop complaints at all. Recently, Westad et al. [147] showed that MU derecruitment is not only promoted by short depressions in contraction amplitude, but also by increased contraction levels. It appears that force variation in either direction promotes derecruitment of MUs.

Although the Cinderella hypothesis gives a plausible explanation for the selective loading of type I muscle fibers, it does not explain the development of muscle fiber damage itself. Possible mechanisms for the development of this damage are reviewed in the subsequent sections.

3.3. Ca^{2+} accumulation

In a recent review by Gissel [38], Ca^{2+} accumulation due to sustained motor unit activity has been suggested to play a causative role in the development of muscle disorders. Long-term low-frequency stimulation (1 Hz, 4 h) caused an increased Ca^{2+} content in rat skeletal muscle cells. The accumulation of Ca^{2+} at this low frequency was much more pronounced in muscles mainly composed of type II fibers. However, a significant increase was also found in the soleus muscle, a muscle consisting of mainly type I fibers. Furthermore, long-term low-frequency stimulation induced leakage of the intracellular enzyme lactate dehydrogenase (LDH) from muscles containing substantial numbers of type II fibers, which indicates membrane damage. No LDH release from the soleus muscle was observed. However, at a higher stimulation frequency (10 Hz) LDH release was found also in the soleus muscle. LDH leakage may reflect degradation of membrane proteins by the Ca^{2+} -activated protease Calpain. This, in turn, leads to further influx of Ca^{2+} and further acceleration of protein breakdown (Fig. 3). Membrane leakages are likely to result in sensations of pain in the damaged muscle.

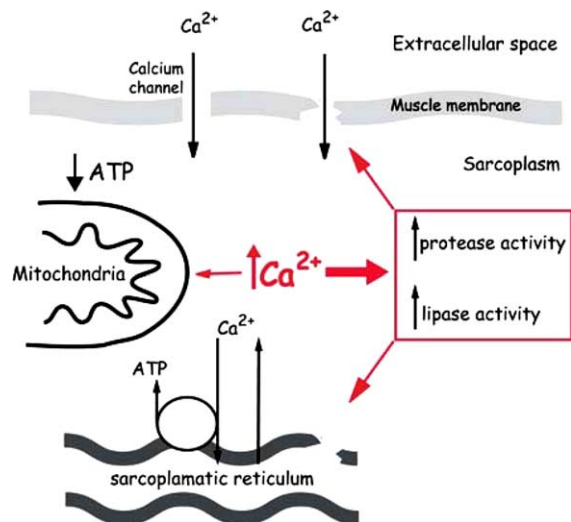


Fig. 3. Accumulation of Ca^{2+} might have noxious effects on the membranes of muscle fibres by stimulating protease and lipase activity. Mitochondrial damage might occur due to mitochondrial Ca^{2+} resorption. For further explanation see text.

Ca^{2+} might play a central role in the development of muscle fiber injury during prolonged muscle activity [36,38,96]. Furthermore, Ca^{2+} accumulation may lead to mitochondrial Ca^{2+} resorption, which has been suggested to result in structural damage and energy depletion.

3.4. Blood supply

3.4.1. Impaired blood flow

Hampering of blood flow and reduction in muscle tissue oxygenation during sustained repetitive work has been suggested to contribute to the development of UEMDs [22,37,76]. The suggestion that local circulatory problems and the consequent disturbances of homeostasis play a role in the development of UEMDs, can also be found in several models proposed to describe the pathophysiology of UEMDs [26,63,64,123,125]. Keller et al. [69], suggest that blood flow can be compromised due to compression of the brachial artery. Postural deviations, often seen in for instance keyboard work (forward displacement of the head and shoulder girdle in combination with scapular protraction), would reduce the cross-sectional area of the thoracic outlet. The resulting compression of the brachial artery has effects distally, including edema, fibrosis, and temperature changes.

A more widely supported explanation for the lack of blood supply is an increased intramuscular pressure, which impedes microcirculation [54,59]. The intramuscular pressure is related to the produced force, the shape and location of the muscle with high pressure at high forces, in cylindrical, and deep muscles [119]. With respect to the muscles involved in UEMDs, substantially

higher pressures were demonstrated in for example, the *M. supraspinatus* (round shaped/located deep under the surface) than in the *M. trapezius* (flatshaped/located at the surface) [53]. Circulation becomes completely blocked when intramuscular pressure exceeds blood pressure. Low-intensity work tasks often involve fairly low levels of intramuscular pressure [53], which would suggest that blood flow is not severely restricted. However, local intra-muscular pressure might be much higher in parts of the muscle where MUs are active than would be expected on the basis of overall muscle activity [124]. This could be the case when type I MUs or mechanically specialized subpopulations of MUs [156] are spatially clustered, such as in muscle compartments that have been identified in animal experiments [151]. In several arm and shoulder muscles, among them the trapezius muscle, indications for compartmentalization have been found [15,50,59,60,92,104]. In addition, prolonged pressure at lower levels (8 h, 30 mmHg) can cause muscle fiber damage at normal blood pressure [46].

The observation that partial obstruction of blood flow occurs at intramuscular pressure levels well below blood pressure is supported by studies that investigated tissue oxygenation [102] and hyper-compensation in blood flow post-exercise [20,21,57,58,113]. For example, Jensen et al. [58] found post-exercise hyperaemia values of two times the resting blood flow even after isometric handgrip exercise at an intensity as low as 2.5% MVC and Røe and Knardahl [113] found such hyperaemia after computer work. Røe and Knardahl [113] do, however, not share the opinion that this post exercise hyperaemia is related to local hypoxia, but suggest that it is centrally mediated. Nevertheless, a recent study found that homeostatic disturbances occur in the trapezius muscle during low-intensity muscle activity, ascribed to local obstruction of blood flow, possibly related to inhomogeneous activation. Contractions at approximately 8% of MVC caused increased K^+ and lactate concentrations, the latter being indicative of anaerobic metabolism [115].

Central adjustment of blood pressure is one of the compensatory mechanisms to optimize blood flow. The increase in blood pressure is dependent on the relative muscle load. In addition, however, activity involving contractions of large muscles trigger a greater blood pressure response than those involving small muscle groups, like forearm muscles [122]. The consequence might be that the blood pressure response will be insufficient in low-intensity arm muscle activities. The inadequate blood flow regulation is possibly linked with the development of pain by a process known as ‘granulocyte plugging’, referring to granulocytes mechanically blocking flow through the capillaries. The combination of vasodilatation as a response to local accumulation of metabolites and a limited blood pressure response might

give granulocytes the opportunity to enter the capillaries and block the micro-circulation. The phenomenon of granulocyte plugging is known from ischemic cardiac disease, but is no more than a hypothesis with respect to UEMDs [122].

Although it seems plausible that suboptimal blood flow (regulation) plays a role in the pathogenesis of UEMDs it remains to be shown whether it is a causal factor itself or an aggravating factor for other causal factors.

3.4.2. Reperfusion injury

Free radicals can cause damage by oxidation of saturated fatty acids in skeletal muscle membranes. Also, oxidation of some proteins including Na^+/K^+ -ATPase and Ca^{2+} -ATPase can take place, resulting in a loss of enzyme activity. The consequences can be membrane damage and disfunctioning of the ion pump of the sarcoplasmic reticulum [96]. Since variations in energy supply are especially large in intermittent concentric contractions, it is expected that the oxygen flux through the tissue and the electron flux through the mitochondrial chain are large also, predisposing to the formation of free radicals in these kinds of activities [96].

3.4.3. Blood vessel–nociceptor interaction

Knardahl [70] proposed a hypothesis on the origin of muscle pain without muscle (cell) activation being the primary cause. He suggests a mechanism, similar to the supposed mechanisms in migraine, in which vessel–nerve interactions play a central role. Knardahl [70] refers to evidence that nociceptive afferent nerves in connective tissue and free nerve endings are located close to the vessel wall of arteries and arterioles. He proposes three options for the interaction: (1) arterial vasodilatation stretches the blood vessel wall, producing mechanical activation; (2) arterial vasodilatation causes vascular production and release of pain producing substances, like bradykinin and nitric oxide, which can activate nociceptors; (3) arterial vasodilatation causes release of inflammatory mediators, such as histamine and substance P and algogenic factors from the plasma that may activate or sensitize nociceptors. Note that this hypothesis is partially conflicting with evidence of an impaired vasodilatation response of the brachial artery to forearm muscle activity in symptomatic subjects observed by Pritchard et al. [110] and the indications that micro-circulation is locally decreased around fibers in the trapezius muscle of subjects with myalgic pain [75,77].

3.5. Muscular force transmission

3.5.1. Myofascial force transmission

Recently, a hypothesis postulating that shear forces between and within muscles can be the cause of muscle

damage has been presented. When contracting muscles apply forces to tendons attached to bony structures, they also apply forces to the surrounding (muscle) tissue (Fig. 4). Especially, when the relative position [87] or change of length of a single muscle (part) is large relative to its environment, substantial shear stresses and strains between muscles or muscle parts are expected to occur [52]. This inter- and extramuscular myofascial force transmission has been predicted to cause a substantial distribution of the lengths of the sarcomeres arranged in series within muscle fibers [153]. Jaspers et al. [56] postulated that local lengthening of sarcomeres could lead to damage, comparable to damage caused by eccentric contractions. In an experiment to verify this, prolonged (3 h) stimulation of a multi-tendoned rat muscle was applied [86]. Intermittent (1 Hz) shortening of a single head of the extensor digitorum longus (EDL) muscle was combined with isometric contractions of the other heads of the EDL and adjacent muscles. Histological analysis revealed muscle damage in all muscles involved. Damaged muscle fibers were predominantly located near the interface with the EDL muscle. It has to be realized that the muscles were activated at a supra-maximal level making it difficult to generalize these results to humans in low-intensity tasks.

Besides the short-term effects, myofascial force transmission might be responsible for adaptations of intramuscular connective tissue with respect to strength and stiffness [55]. Interventions with the myotendinous force transmission of rat m. extensor digitorum longus (EDL) by tenotomy and aponeurotomy showed variations in strength of the intramuscular connective tissue at the interface between heads of the multi-tendoned EDL. Jaspers et al. [55] suggested that, in humans performing frequent isolated finger movements as in keying or playing an instrument, local shear and stress deformations will initiate adaptations of the intramuscular connective

tissue in such a way that independent finger movements become restricted. To prevent undesired digit movements, co-activation of antagonists and intrinsic muscles might be required. Leijnse [78,79], who focused on the intertendinous connections between muscle heads, similarly suggested that this anatomical limitation of independent finger movements ultimately leads to increased muscle activation in certain tasks where these movements are required and thus to an increased risk for ‘overuse’ of muscles.

3.5.2. Intramuscular shear forces

With respect to the role of shear stresses in low-intensity tasks, Vøllestad and Røe [141] have suggested that low-intensity static contractions lead to higher shear loading than high-intensity dynamic contractions. Their argument is that only a small fraction of the muscle fibers within a muscle contracts during low-intensity contractions. Due to low-firing rates in these situations MUs generate oscillating forces. Furthermore, MU shortening and lengthening is not synchronized, contributing to the movement of fibers with respect to each other. The nociceptors located between the muscle fibers are exposed to repetitive shear stresses under these conditions. Finally, the shear stresses may increase with duration of work as the amplitude of the oscillations increases during prolonged repetitive contractions.

To our knowledge, there are no experimental data to support the notion that this shear stress mechanism actually produces nociception and or damage.

3.6. Trigger points

Mense and Simons [99] argue that trigger points (TrPs) are not just signs of myalgia, but that they play a causal role in the development of UEMDs. TrPs are very common with prevalences of up to 50% in neck/shoulder muscles. The presence of TrPs is not always accompanied by symptoms. Mense and Simons distinguish between latent and active TrPs with the only difference the occurrence of spontaneous pain in the active TrPs. Both latent and active TrPs can be defined as hyperirritable nodules of spot tenderness in a palpable taut band of skeletal muscle [121].

TrPs are located near the insertion of the muscle or in the motor endplate area. The relevance of TrPs as causal factor is mainly based on the finding that muscle pain disappears when TrPs are removed by effective therapy. In a recent review, Simons [121] describes a hypothesis on the development of TrPs. In short, the hypothesis postulates that a TrP has multiple muscle fibers with endplates releasing excessive Acetylcholine (Step 1), accompanied by regional sarcomere shortening (Step 2, Fig. 5). The shortened sarcomeres have unusually high oxygen demands, while the increased tension likely compromises circulation producing local ischemia

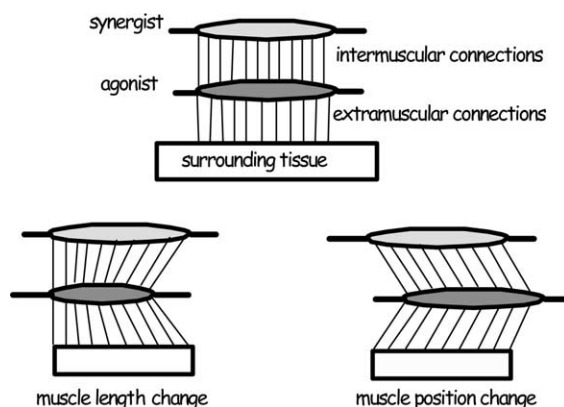


Fig. 4. Schematic presentation of configuration changes in inter- and extramuscular connections involved in myofascial force transmission. The effect of both muscle length change and muscle position change are illustrated.

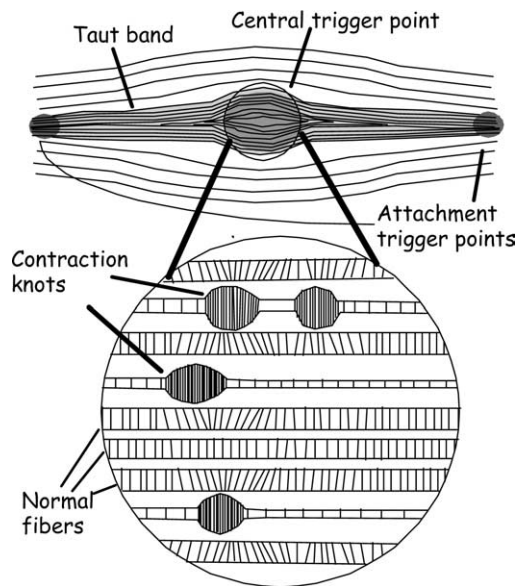


Fig. 5. Schematic presentation of trigger points in a palpable taut band of skeletal muscle. The magnification of the central trigger point shows contraction knots in some of the muscle fibers (based on [121]). For further explanation see text.

(Step 3). Ischemia and local hypoxia could lead to tissue distress: as appears from a reduction of ATP and release of sensitizing substances (Step 4). The sensitizing substances are responsible for the sensitization of nociceptors (Step 5), leading to pain. Some of the steps in the trigger point hypothesis overlap with the previously mentioned theories. Dysfunctioning of the endplates is exclusive for this hypothesis and especially this part of the hypothesis has some uncertainties with respect to a possible causal role of muscle activity and task requirements. Mense and Simons [99] and Simons [121] mention that the step from latent TrPs to active TrPs is under the influence of an autonomic central process, but at the same time they argue that it can be triggered by a rather broad range of muscle activities leading to muscle overload.

3.7. Impaired heat shock response

Forde et al. [32] formulated the hypothesis that disruption of the heat shock response could lead to pathogenic levels of chaperone proteins causing cell death. The hypothesis is based on the observation that exposing cells to stress – either heat stress, oxygen stress as occurs in inflammatory responses, or ischemic conditions – leads to an increased production of chaperone proteins. Under normal conditions a self-limiting feedback loop exists in which chaperones shut down their own production. However, as cells age, either naturally or prematurely due to adverse external exposures, the heat shock response does not function properly leading to

harmful levels of chaperones. Forde et al. [32] themselves indicate a lack of information on the relationship between occupational muscle activity and the level of cellular stress as a weak point in this theory.

4. Feedback loops from muscle disorder to muscle activity

The understanding of the pathophysiological process from muscle activity to disturbances of physiological processes in the body and disorders of the muscle(s) is crucial, but as indicated in Section 2 does not necessarily clarify the occurrence of the symptoms. It is possible that a minor disorder of muscle tissue creates a loop feeding back onto muscle activity, thus creating a vicious circle in the model of Fig. 1. Such a vicious circle could aggravate the initial disorder and eventually lead to symptoms. Hypotheses regarding the occurrence of such loops will be discussed in this section.

Nociceptive afference may be the consequence of muscle activity but can in turn play a role in muscle activation. Johansson and Sojka [62] proposed that the γ -muscle spindle system plays a central role in a self-maintaining 'vicious circle' in which nociception and muscle activity amplify each other. Muscle contractions produce metabolites and low pH, which activates nociceptive types III and IV muscle afferents, which in turn activate the γ -motor neurons. Elevated γ -motor neuron activity would cause elevated muscle spindle activity, which in turn would increase muscle fiber activity and stiffness. The positive feedback loop might also reinforce the activity of surrounding muscles, explaining the spreading of complaints to neighboring muscles (Fig. 6). Recent studies have not provided unambiguous

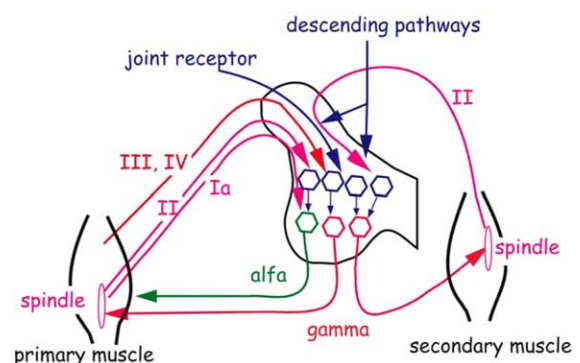


Fig. 6. The possible role of the γ -muscle spindle system in a self-maintaining 'vicious circle': muscle contraction produces metabolites and reduces pH, which can activate nociceptive types III and IV muscle afferents, which in turn activate the γ -motor neurons. Elevated γ -motor neuron activity would cause elevated muscle spindle activity, which in turn would increase muscle fiber activity and stiffness. The positive feedback loop might also reinforce the activity of surrounding muscles.

support for this theory. An increased output of muscle spindles in cat hind leg and neck muscles, as a consequence of nociceptive stimuli, was found in a range of experiments [25,84,108,106]. Evidence of hyperexcitability of the α -motor neuron pool after noxious stimulation of muscle was found in cats and rats [105,130,143]. In contrast, an experiment in which myositis was induced in the hind leg of the cat showed a decreased activity of γ -motor neurons [100]. Also in cat back muscles, no increased γ -motor neuron activity was found after injection of bradykinin and capsaicin [68]. Experimental results in humans are sparse. In human calf and masticatory muscles, the stretch reflex, which is mediated by muscle spindle afferents, was found to be enhanced after injection of hypertonic saline [95,131]. However, in back muscles no enhancement of stretch reflexes was found after hypertonic saline injection [154]. In addition, during walking the stretch reflex in the calf muscles was unaffected by induced pain [94]. The amplitude of the Hofmann's reflex, which is an indicator of α -motor neuron excitability, was not increased after injection of hypertonic saline in the calf muscles [95] and Farina et al. [30] found even reduced firing rates of motor units after induction of pain. However, resting EMG levels were increased in human masticatory muscles during induced pain [130], although the effect was only short-lived. In conclusion, a direct effect of pain on muscle activity leading to a vicious circle is not consistently supported by the literature.

Recently, a more indirect feedback mechanism of pain on muscle activity has been proposed [61]. The proposed loop consists of a negative effect of nociception on proprioception leading to less precise control of movement that if the task requirements call for this could be compensated through increased co-contraction thus increasing muscle activity. In animal studies, increased types III and IV afferent activation did diminish the information content of muscle spindle afference [106,135]. Also in humans, muscle fatigue has been shown to negatively affect proprioception [11,33,107]. Furthermore, patients with pain in the cervical region were shown to display an impaired ability in a head-repositioning task [112]. A recent reformulation of the hypothesis of Johanssen and Sojka focuses on this aspect, where it is assumed that the reduced proprioception requires increased effort to maintain task performance, which might lead to a vicious circle [61]. Results from animal studies indicate that, in addition to the peripheral effects on sensory quality, changes in the cerebral cortex as a response to sustained repetitive muscle activity can occur [17–19]. In monkeys that performed highly stereotypical and spatially constrained and highly repetitive movements with one hand, changes in the cerebral cortex suggest a reduction in the differentiation of sensory information from the hand and arm [19]. It is therefore possible that pain impairs proprio-

ception, which will lead to less precise motor control and possibly as a compensatory reaction, to an increased effort mainly in the form of increased co-activation of muscles. Increased muscle activation and especially a lack of relaxation as shown in patients with UEMDs [28,73] and whiplash associated disorders [103], and increased pen pressure during a graphical aiming task in patients with a-specific forearm pain [13] support this assumption.

5. Discussion

This review focused on the injury mechanisms that could underlie upper extremity muscle disorders. In Section 2, it was found that several studies have provided evidence for the presence of muscle tissue disorders (muscle fiber abnormalities and impaired micro-circulation) in people with UEMDs. It was concluded that these disorders are not a sufficient condition for complaints to occur but yet may play a causal role. Section 3 focused on the question how these disorders may develop. The following mechanisms were discussed: (1) Cinderella motor-units loading; (2) Ca^{2+} accumulation; (3a) impaired blood flow; (3b) reperfusion injury; (3.3c) blood vessel–nociceptor interaction; (4a) myofascial force transmission; (4b) intramuscular shear forces; (5) trigger points; (6) impaired heat shock response. The literature shows no complete proof for any of these mechanisms. Some mechanisms have been studied quite extensively and have received partial support. Other mechanisms have hardly been studied yet.

As expected, none of the hypotheses included in Section 3 is able to explain when muscle activity can become pathogenic to its full extent. However, three scenarios emerge. First, sustained (usually low-intensity) muscle activity is likely to coincide with selective and sustained activation of type I motor units as proposed in the Cinderella hypothesis. This may lead to Ca^{2+} accumulation in the active motor units and other homeostatic disturbances due to limitations in local blood supply and metabolite removal in muscle compartments with larger numbers of active MUs. The key-factor in this scenario is the duration of continuous muscle activity, although an interaction effect with activity level is likely to occur. Note that an independent mechanism proposed (nociceptor sensitization due to intra-muscular shear forces) also suggests that long periods of low-level activity may lead to disorders, but this mechanism is less well supported by the literature. Second, intermittent activity (especially of high-intensity) may trigger mechanisms, such as reperfusion injury and blood-vessel nociception interaction. The key-factor in this scenario is the fact that muscle activity is of relatively high intensity and intermittent, which leads to frequent and strong changes of blood flow into the muscle.

Third, when intermittent activity coincides with selective length changes of muscle parts relative to their environment, local sarcomere lengthening due to myofascial force transmission may lead to injury. The key-factor in this scenario is the repetitive length change of single muscle parts or muscles. The bulk of the findings from the biopsy studies reviewed in Section 2, which indicate mitochondrial dysfunction of type I fibers in myalgic muscles and reduced micro-circulation, are in line with the first scenario. Overall the first scenario is best supported by empirical data and appears to fit well with epidemiological data on UEMDs. The second and third scenario have hardly been investigated and thus cannot be refuted nor supported.

Johansson et al. [61] concluded that the multiple individual mechanisms interact in (series of) circular processes, with the implication that it is unlikely to pinpoint a unique causal starting point. In our simple model we chose the muscle activity as a starting point. This has heuristic value for the prevention of UEMDs and is supported by consistent relationships between physical exposures and incidence of UEMDs [2,7,14,16,42,89,126,128]. However, to illustrate some of the circular processes potentially involved, consider the following: The homeostatic disturbances in muscle, resulting from muscle activity, can result in an accumulation of metabolites, stimulating nociceptors. This process can be enhanced in subjects with relatively large type I fibers and low capillarization, which paradoxically may have developed as an adaptation to the exposure. Nociceptor activation can disturb the proprioception and thereby the motor control most likely leading to further increased disturbance of muscle homeostasis. The pain resulting from nociceptor activity can cause increased sympathetic activity leading to decreased muscle circulation and increased levels of muscle activity. In addition, in the long run a reduction of the pain threshold and an increase of pain sensitivity can develop. It is worth noting that initial nociceptor stimulation may be a response to metabolite accumulation preceding tissue damage.

As indicated in Fig. 1, the pathophysiological process is under the influence of effect modifiers, varying from individual to psychosocial factors. Task stress has an influence on all levels of the model. It has an effect on the relationship between task requirements and muscle activity [140], with task stress having an increasing effect on muscle activation. Stress can also have a negative effect on circulation and oxygen supply to the muscles by sympathetic influence and hyperventilation [118]. In addition, hormonal effects of stress may lead to a decreased anabolic capacity, which would negatively affect tissue quality and the capacity to regenerate tissue after injury [133]. Finally stress has an influence on the relation between disorders and symptoms, the sensation of pain and illness related behavior. Pain itself is a power-

ful stressor, so a reciprocal reinforcement is likely to occur. Obviously, a multitude of individual factors may have substantial influence on the relations in the model in Fig. 1. For example, muscle activation levels differ widely between subjects performing the same tasks [91]. With respect to UEMDs the individual pain tolerance seems to be a relevant source of inter individual variation [88]. This individual pain tolerance seems, however, less determined by genetic than by situational, psycho-social factors [12].

The literature reviewed here indicated that objectifiable peripheral disorders could underlie UEMDs, although a one to one relationship between disorders and symptoms has not been shown. Perhaps the latter is hardly to be expected given the important role of a range of effect modifiers of both situational and individual nature. Furthermore, the literature provides some tentative but plausible mechanisms that could cause these disorders. Preventive and therapeutic efforts could be designed on the basis of these mechanisms. Effectiveness of this approach of course remains to be shown.

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